Remarks / Arguments

Applicants cancel claims 41, 43-47, 49, 51-77, 79, and 80; amend claims 38, 40, 42, 48, 50 and 78; and provide new claims 81-95.

Support for Amendments

Support for the amendments may be found throughout the application as filed. Exemplary passages are provided for each amendment for the convenience of the examiner.

Claim 38 is amended to recite a transformed bryophyte cell from *Physomitrella patens* that comprises i) a disrupted fucosyl transferase nucleotide sequence and ii) a disrupted xylosyl transferase nucleotide sequence, wherein the bryophyte cell is incapable of forming N-linked glycans with 1,3-linked fucosysl and 1, 2-linked xylosyl residues. Support may be found on page 1, line 4-6, which provides,

> "The present invention relates to a method for producing heterologous glycosylated proteins in bryophyte cells, such as in transformed *Phsycomitrella pate*ns cells."

Additional support may be found on page 7, lines 16-22 of the present application,

> "Dysfunctional" as used herein means that the nominated transferase nucleotide sequences of fucosyl transferase (fucT) and xylosyl transferase (xylT) are substantially incapable of encoding mRNA that codes for functional fucT and xylT proteins that are capable of modifying plant N-linked glycans with plant like glycosylation patterns comprising 1,3 linked fucosysl and 1, 2 linked xylosyl residues."

Further support may be found on page 7, lines 22-25, which provides, "In a preferment, the dysfunctional fucT and xylT plant transferase nucleotide sequences comprise targeted insertions of exogenous nucleotide sequences" and page 7, line 35-36, which provides, "In a

further preferment, the dysfunctional fucT and xylT plant transferase nucleotide sequences may comprise targeted deletions[.]" Further support may be found on page 11, lines 2-3, which provides, "[T]he expression of the sequences is substantially impaired if not completely disrupted."

Claim 40 is amended to recite the glycosylated polypeptide comprises a human glycosylation pattern. Support may be found on page 6, lines 19-22, which provides,

> "It is an object of the present invention to provide a more efficient method of producing animal proteins comprising animal glycosylation patterns, and in particular, glycosylated human proteins comprising human glycosylation patterns thereon."

Claim 42 is amended to recite the nucleotide sequence encodes a functional human beta 1, 4 galactosyltransferase that is expressed in the bryophyte cell. Support may be found on page 9, lines 12-15, which provides,

> "In a further preferment, the mammalian galactosyl transferase nucleotide sequence is a beta 1, 4 galactosyltransferase (beta 1,4 galT) and most preferably is a human beta 1, 4 galactosyltransferase nucleotide sequence."

Claim 48 is amended to delete recitations of nonhuman species.

Claim 50 is amended to correct markush group claim language.

Claim 78 is amended to clarify the dependency.

Claim 81 is newly added, depends from claim 38 as amended, and recites the disrupted fucosyl transferase nucleotide sequence and the disrupted xylosyl transferase nucleotide sequence are each independently disrupted by insertion of exogenous nucleic acids or by at least partial deletion of endogenous nucleic acids. Support may be found on page 7, lines 22-25, which provides, "In a preferment, the dysfunctional fucT and xylT plant transferase nucleotide sequences comprise targeted insertions of exogenous nucleotide sequences." Further support may be found on page 7, line 35 through page 8, line 5, which provides,

> "In a further preferment, the dysfunctional fucT and xylT plant transferase nucleotide sequences may comprise targeted deletions of the whole or substantially the whole endogenous gene sequences thereof, or indeed, targeted partial deletions of the endogenous gene sequences of fucT and xylT nucleotide sequences, thus rendering such sequences dysfunctional within the context of the invention."

Claims 82 and 94 are newly added and provide the glycosylated peptide is selected from the group consisting of an interferon, a fertility hormone, a growth factor and an enzyme. Support may be found on page 8, lines 20-35, which provides,

> "Such pharmaceutical glycoproteins for use in mammals, including man include but are not limited to proteins such as ...interferons...fertility hormones...growth factors. . .enzymes[.]"

Claims 83 and 89 are newly added and set forth the limitation provided in claim 42 as amended.

Claims 84 and 91 are newly added and set forth the limitation provided in claim 40 as amended.

Claims 85 and 92 are newly added and set fort the limitation provided in claim 48 as amended.

Claims 86 and 93 are newly added and set forth the limitation provided in claim 50 as amended.

Claims 87 and 95 are newly added and set forth the limitation provided in claim 78 as amended.

Claim 88 is newly added and provides a transformed bryophyte cell from *Physomitrella patens* that comprises a double knockout of fucosyl transferase and xylosyl transferase that results in modified N-glycans without detectable 1, 3-linked fucosyl and 1, 2-linked xylosyl residues. Support may be found as provided above with respect to claim 38 as amended. Further

support may be found on page 6, lines 1-4, which provide, "Moreover, the double knockout of FucT and XylT resulted in modified N-linked glycans without detectable 1,3 linked fucosyl and 1,2 linked xylosyl residues."

Claim 90 is newly added and sets forth the limitation provided in claim 39, which was previously presented.

Introduction of the Invention

The present invention is directed towards a transformed bryophyte cell from *Physcomitrella patens*. In the first set of claims, the transformed bryophyte cell includes a disrupted fucosyl transferase nucleotide sequence and a disrupted xylosyl transferase nucleotide sequence. The result is a bryophyte cell that does not provide 1, 3-linked fucosyl and 1, 2-linked xylosyl residues, which are associated with plant glycosylation patterns. In further embodiments, a functional human beta 1, 4 galatosyltransferase is expressed within the transformed bryophyte cell. Accordingly, in some embodiments the transformed bryophyte cell provides glycosylation reactions like those occurring in humans but not naturally in bryophytes.

The second set of claims, which begins with new independent claim 88, provides a transformed bryophyte cell from *Physcomitrella patens* that comprises a double knockout of fucosyl transferase and xylosyl transferase that results in modified N-glycans without detectable 1, 3-linked fucosyl and 1, 2-linked xylosyl residues. The result is a double knockout without detectable 1, 3-linked fucosyl and 1, 2-linked xylosyl residues, which are associated with plant glycosylation patterns. Like the first group introduced above, in further embodiments a functional human beta 1, 4 galatosyltransferase is expressed within the transformed bryophyte cell and thus glycosylation reactions like those occurring in humans but not naturally found in bryophytes may be performed.

Response to Objections

I.

Objections to Abstract

The Examiner has objected to the abstract as not being on a separate sheet of paper. Applicants provide herewith the abstract presented on a separate sheet of paper. Accordingly, Applicants respectfully request the objection be withdrawn.

II.

Claim Objections

With respect to claims 45-47, the Examiner has objected to the term "Physcomitrella ..." without italics and suggest amending the claims to include italics. Applicants have amended each recitation as "*Physcomitrella...*"

With respect to claim 50, the Examiner indicates claim 50 contains the abbreviation VEGF in the claim and suggests at least in the first recitation of abbreviations, expanding them to recite the full forms of what the abbreviations stand for. Applicants amend claim 50 to include the expansion of VEGF, namely vascular endothelial growth factor.

Applicants respectfully request all objections be withdrawn.

Response to Claim Rejections 35 U.S.C. § 112

I.

Indefinite Rejections

Claims 38-50, and 78

The examiner rejected claims 38-50 and 78 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention. Specifically, it is unclear to the examiner as to what makes a nucleic acid sequence which is incapable of encoding an active fucosyl transferase or xylosyl transferase a "dysfunctional transferase or a dysfunctional transferase gene" and argues one cannot define something by saying what it lacks.

Applicants cancelled claims 41, 43-47 and 49 and have amended claim 38, from which claims 39, 40, 42, 48, and 78 depend to recite the bryophyte cell comprises a disrupted fucosyl transferase nucleotide sequence and a disrupted xylosyl transferase nucleotide sequence. Further, the bryophyte cell is incapable of forming N-linked glycans with 1,3-linked fucosysl and 1, 2-linked xylosyl residues.

Amended claim 38 provides structural features that define the invention. Specifically, claim 38 provides disrupted fucosyl transferase and xylosyl transferase nucleotide sequences, which are structurally different from endogenous or native sequences. Accordingly, a transformed bryophyte cell having these structural features results in the inability to form N-linked glycans with 1, 3-linked fucosyl and 1, 2-linked xylosyl residues. Since the recitations provided are definite, applicants respectfully request the rejection be withdrawn.

Claims 40 and 41

The examiner rejected claims 40 and 41 under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, it is unclear to the examiner as to what biological or chemical characteristics define an "animal glycosylation pattern" or "mammalian glycosylation pattern" and what structural limitations the claimed broyphote cell must have to be encompassed within the scope of these limitations.

Applicants have cancelled claim 41 and amended claim 40 to recite the glycosylated polypeptide includes a human glycosylation pattern. In determining the meaning of patent claims, words or phrases in a claim are given their ordinary meaning unless the specification indicates the inventor used the words or phrases differently. Smith & Nephew, Inc. v. Ethicon, Inc., 376 F.3d 1304, 61 USPQ2d

1065, 1069 (Fed. Cir. 2002). Further if the claims, read in light of the specification, reasonably apprise those skilled in the art of the use and scope of the invention, and if the language is as precise as the subject matter permits, the claims are definite under Section 112, second paragraph. Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624 225 USPQ 634, 641 (Fed. Cir.) *cert. dismissed*, 474 U.S. 976 (1985).

One skilled in the art would understand a human glycosylation pattern as a series of glycosylation residues positioned along a polypeptide in a manner consistent with human expression of the same polypeptide. Specific human glycosylation patterns are available to those skilled in the art through databases such as SWISS-PROT. Further, this is consistent with the specification, which provides a double knockout that inhibits plant-specific glycosylation reactions and optionally includes enzymes that glycosylate polypeptides as provided in humans. Since human glycosylation patterns are known in the art applicants are not required to provide a complete listing of all glycosylation modifications. However, applicants have provided exemplary human glycosylation patterns. Specifically, a human glycosylation pattern may include terminal beta 1, 4 galactose residues formed by human beta 1, 4 galactosyltransferase. Similarly, a human glycosylation pattern would not include 1, 3 fucosyl or 1, 2 xylosyl residues since these are not found naturally in humans. Accordingly, applicants respectfully request the objection be withdrawn.

Claim 50

Claim 50 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the examiner is unclear whether recitations in the claim are merely exemplary or required. Applicants have amended the markush group of claim 50, which renders the claim definite. Accordingly, applicants request the rejection of claim 50 be withdrawn.

II.

Enablement Rejections

The examiner rejected claims 38-50 and 78 under 35 U.S.C. § 112, first paragraph, as not being enabled. Specifically, the examiner argues the specification does not reasonably provide

enablement for a) any transformed bryophyte, b) wherein said bryophytes comprise a dysfunctional (impaired) FucT and XylT and c) said bryophytes comprising and encoding any galactosyltransferase from any source including variants, mutants and recombinants and capable of producing any mammalian glycosylation pattern.

The examiner acknowledges the specification does sufficiently enable: a) the specific bryophyte *Physcomitrella patens*, wherein in *Physcomitrella patens* the endogenous gene encoding for alpha 1, 3 fucosyltransferase (FucT) and the endogenous gene encoding for beta 1, 2 xylosyltransferase (XylT) have been disrupted through targeted insertion, thus disrupting the coding regions of said genes; b) within the double knockout, the gene encoding the human beta 1, 4-galactosyltransferase catalyzing the following glycosylation patten; UDP-galactose + N-acetyl-glucosaminylglycopeptide ↔ UDP + beta-D-galactosyl 1, 4-N-acetylbeta-D-glucosaminylglycopeptide (GalT, GenBank X55415) has been integrated by homologous recombination; and c) said *Physcomitrella patens* comprising said gene double knockout (FucT and XylT) and expressing the human galT is transformed with an expression construct encoding the secretable/soluble form of human vascular endothelial growth factor (VEGF).

The enablement requirement is met when the specification teaches one of ordinary skill in the art how to make and use the invention. The general policy of the enablement requirement is to ensure the claimed invention is communicated in such a way that the public may understand and perhaps build on it. However, a detailed report regarding how to make and use the invention is unnecessary if a person of ordinary skill in the art could understand the invention without such an explanation. For instance the CCPA has stated that "not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." In re Gay, 309 F.2d 769, 135 USPQ 311, 316 (C.C.P.A. 1962). This is consistent with the discussion provided in Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 56 USPQ2d 1332, 1336 (Fed. Cir.), *cert denied*, 532 U.S. 1019 (2001), which stated,

> "Requiring inclusion in the patent of known scientific/technological information would add an imprecise and open-ended criterion to the content of patent specifications, could greatly enlarge the content of patent specifications and unnecessarily increase the cost of preparing and prosecuting patent applications,

> and could tend to obfuscate rather than highlight the contribution to which the patent is directed. A patent is not a scientific treatise, but a document that presumes a readership skilled in the field of the invention."

In addition, there is no requirement that, for a patent claim to be enabled, it must enable all embodiments of the invention. On the contrary, the CCPA and Federal Circuit have both recognized that a claim need not enable all embodiments of the invention. Instead, to be enabling, the specification must teach those skilled in the art how to make and use the invention without undue experimentation. Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPTO2d 1001, 1004 (Fed. Cir.), *cert. denied*, 522 U.S. 963 (1997).

A. All pending claims are directed towards a transformed bryophyte cell from *Physcomitrella patens*

The examiner argues the specification does not provide enablement for any transformed bryophyte cell but does provide enablement for the bryophyte *Physcomitrella patens*. The specification discusses a variety of bryophytes including *Physcomitrella, Funaria, Sphagnum, Ceratodon, Marchantia* and *Sphaerocarpos*, such as on page 7. However, to expedite allowance of the present application applicants have amended claim 38 to recite the bryophyte cell is from *Physcomitrella patens*. Accordingly, applicants respectfully request the rejection be withdrawn.

Similarly, new independent claim 88 provides a transformed bryophyte cell from *Physcomitrella patens* that comprises a double knockout of fucosyl transferase and xylosyl transferase that results in modified N-glycans without detectable 1, 3-linked fucosyl and 1, 2-linked xylosyl residues. Accordingly, claim 88 also recites the bryophyte cell is from *Physcomitrella patens*. Thus, applicants also respectfully request allowance of claim 88 and the claims that depend from claim 88.

B. Independent claim 38 is directed towards a transformed bryophyte cell comprising disrupted fucosyl transferase and xyolosyl transferase nucleotide sequences and new independent claim 88 is directed towards a transformed bryophyte cell comprising a double knockout of fucosyl transferase and xylosyl transferase

The examiner argues the specification does not provide enablement for a bryophyte cell including dysfunctional (impaired) fucosyl transferase and xylosyl transferase nucleotide sequences but does provide enablement for a bryophyte including endogenous genes encoding for alpha 1, 3 fucosyltransferase (FucT) and the beta 1, 2 xylosyltransferase (XylT) disrupted through targeted insertion. For clarity, applicants have amended claim 38 to recite the transformed bryophyte cell includes a disrupted fucosyl transferase nucleotide sequence and a disrupted xylosyl transferase nucleotide sequence, wherein the bryophyte cell is incapable of forming N-linked glycans with 1,3-linked fucosysl and 1, 2-linked xylosyl residues. Disruption of fucosyl transferase and xylosyl transferase nucleotide sequences including insertion of exogenous nucleotide sequences is discussed on page 7; and deletion of endogenous nucleotide sequences is discussed on pages 7-8. Thus, applicants respectfully request the rejections be withdrawn.

For completeness, new independent claim 88 provides a transformed bryophyte cell from *Physcomitrella patens* that comprises a double knockout of fucosyl transferase and xylosyl transferase that results in modified N-glycans without detectable 1, 3-linked fucosyl and 1, 2-linked xylosyl residues. Accordingly, claim 88 recites the bryophyte cell includes a double knockout of fucosyl transferase and xylosyl transferase, which is discussed throughout the specification. Thus, applicants also respectfully request allowance of claim 88 and the claims that depend from claim 88.

C. Claims 42, 83 and 89 provide a transformed bryophyte that encodes a functional human 1, 4 beta galactosyltransferase

The examiner argues the specification does not provide enablement for a bryophyte cell including any galactosyltransferase from any source but acknowledges the specification does

teach a bryophyte cell encoding the human beta 1, 4-galactosyltransferase. Although one skilled in the art with the present disclosure would be able to express within a bryophyte cell, many functional enzymes involved in mammalian glycosylation using recombinant techniques, to expedite allowance applicants have amended claim 42 to recite the transformed bryophyte cell encodes a functional human beta 1, 4 galatosyltransferase that is expressed in the bryophyte cell. Accordingly applicants respectfully request the rejection be withdrawn.

Similarly, new claims 83 and 89 recite the transformed bryophyte cell encodes a functional human beta 1, 4 galatosyltransferase that is expressed in the bryophyte cell. Thus, applicants also respectfully request new claims 83, 89 and corresponding dependent claims be allowed.

III.
Written Description Rejections

The examiner rejected claims 38-50 and 70 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The examiner argues there are no structural limitations recited in the claims with regard to a) the members of the Division of bryophytes comprising a dysfunctional FucT or XylT or both; and b) said bryophytes comprising a genius of mammalian galactoyltransferases from any source including variants, mutants and recombinants and capable of producing any mammalian glycosylation pattern. Each is addressed below with respect to the claims as amended.

A. Independent claim 38 and new claim 88 recite the bryophyte cell is from *Physocomitrella patens*

Applicants have demonstrated the present invention is adaptable to bryophytes that include FucT and XylT as part of the native genome. Among these are included *Physcomitrella, Funaria, Sphagnum, Ceratodon, Marchantia* and *Sphaerocarpos.* However, to expedite allowance of the present invention, applicants have amended claim 38 to including the bryophyte

cell is from *Physcomitrella patens*. Accordingly, applicants respectfully request the rejections be withdrawn.

Similarly, applicants provide new independent claim 88, which provides a transformed bryophyte cell from *Physcomitrella patens* that comprises a double knockout of fucosyl transferase and xylosyl transferase that results in modified N-glycans without detectable 1, 3-linked fucosyl and 1, 2-linked xylosyl residues. Accordingly, claim 88 and its dependent claims recite the specific bryophyte *Physcomitrella patens*, and applicants also request allowance of claim 88 and its dependent claims.

B. Amended claim 38 and new claim 88 clarifies structural features of FucT and XylT

The Examiner indicates the claims lack structural features regarding a dysfunctional FucT and XylT. With respect to claim 38, the bryophyte cell from *Physcomitrella patens* includes disrupted fucosyl and xylosyl transferase nucleotide sequences and the bryophyte cell is incapable of forming N-linked glycans with 1,3-linked fucosysl and 1, 2 linked xylosyl residues. Since disrupted nucleotide sequences are structurally different than native sequences, specific structural features are provided. Accordingly, applicants respectfully request the rejection be withdrawn.

Similarly, new claim 88 provides a double knockout of fucosyl transferase and xylosyl transferase that results in modified N-glycans without detectable 1, 3-linked fucosyl and 1, 2-linked xylosyl residues. Thus, claim 88 provides a knockout, which is structurally different from a native sequence. Applicants respectfully request allowance of claim 88 and its dependent claims.

C. Claims 42, 83 and 89 recite a functional human beta 1, 4 galactosyltransferase

Although the specification supports multiple enzymes deemed a galactosyltransferase, to expedite allowance of the present invention, applicants have amended claim 42 to include the nucleotide sequence encodes a functional human beta 1, 4 galactosyltransferase. As such, a

transformed bryophyte cell that expresses a functional human beta 1, 4 galactosyltranferase is capable of performing glycosylation reactions like those found in humans. Accordingly, applicants respectfully request the rejections be withdrawn.

Similarly, new claims 83 and 89 recite a functional human beta 1, 4 galactosyltransferase. Thus, applicants respectfully request allowance of claims 83, 89 and any corresponding dependent claims.

In view of the amendments and arguments set forth above, Applicants respectfully request a Notice of Allowance be issued for the instant application.

Respectfully submitted,

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Date

Raymond Wagenknecht
Reg. No. 50,948

Biotech Beach Law Group PC
625 Broadway, Ste 1210
San Diego, CA 92101
(619) 238-1179